	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
11	BRS	L11	326	heparin adj cofactor adj II	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/09 07:10			0
12	BRS	L12	153	protein adj c adj inhibitor	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/09 07:12			0
13	BRS	L13	1386	platelet adj factor$14	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/09 07:13			0
14	BRS	L14	225	bovine adj pancreatic adj trypsin adj inhibitor	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/09 07:14			0
15	BRS	L15	6	ghilanten$1related adj inhibitor	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/09 07:15			0
16	BRS	L16	18	7 same (8 or 9 or 10 or 11 or 12 or 13 or 14 or 15)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/09 07:17			0
17	BRS	L17	0	16 same 6	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/09 07:16			0
18	BRS	L18	0	7 same 6	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/09 07:17			0
19	BRS	L19	177	heparin$1binding adj domain	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/09 07:17			0
20	BRS	L20	8	19 same (8 or 9 or 10 or 11 or 12 or 13 or 14 or 15)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/09 07:17			0
21	BRS	L21	0	20 same 6	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/09 07:17			0

	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
1	BRS	L1	4	((TFPI or TFPI-2) same ((kunitz same (domain adj TFPI)) or (kunitz same (domain adj TFPI-2)))) same (chimeric or fusion)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/09 07:06			0
2	BRS	L2	407	TFPI	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/09 07:06			0
3	BRS	L3	50	TFPI-2	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/09 07:06			0
4	BRS	L4	42	2 same 3 same kunitz same domain	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/09 07:07			0
5	BRS	L5	24473	(chimeric or fusion) adj protein	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/09 07:08			0
6	BRS	L6	9	4 same 5	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/09 07:08			0
7	BRS	L7	315	heparin adj binding adj domain	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/09 07:16			0
8	BRS	L8	343	protease adj nexin$1	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/09 07:09			0
9	BRS	L9	343	protease adj nexin$12	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/09 07:09			0
10	BRS	L10	2155	antithrombin adj III	USPAT; US-PGPUB; EPO; JPO; DERWENT	2002/12/09 07:10			0

=> d his

(FILE 'HOME' ENTERED AT 07:20:19 ON 09 DEC 2002)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
07:21:46 ON 09 DEC 2002
L1 3355 S TFPI OR TFPI-2
L2 1746 S KUNITZ (P) DOMAIN
L3 354 S L1 (P) L2
L4 4 S L3 (P) (CHIMERIC PROTEIN)
L5 2 S L3 (P) (FUSION PROTEIN)
L6 4 S L4 OR L5
L7 4 DUPLICATE REMOVE L6 (0 DUPLICATES REMOVED)
L8 2925 S HEPARIN BINDING DOMAIN
L9 37901 S (PROTEASE NEXIN-1) OR (PROTEASE NEXIN-2) OR (ANTITHROMBIN III
L10 12786 S (PLATELET FACTOR 4) OR (BOVINE PANCREATIC TRYPSIN INHIBITOR)
L11 158 S L8 (P) (L9 OR L10)
L12 0 S L7 (P) L11

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FILE 'HOME' ENTERED AT 07:20:19 ON [redacted] DEC 2002

=> file medline caplus biosis embase scisearch agricola
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.63       0.63

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FILE 'AGRICOLA' ENTERED AT 07:21:46 ON 09 DEC 2002

=> s TFPI or TFPI-2
L1         3355 TFPI OR TFPI-2

=> s kunitz (p) domain
L2         1746 KUNITZ (P) DOMAIN

=> s l1 (p) l2
L3          354 L1 (P) L2

=> s l3 (p) (chimeric protein)
L4            4 L3 (P) (CHIMERIC PROTEIN)

=> s l3 (p) (fusion protein)
L5            2 L3 (P) (FUSION PROTEIN)

=> s l4 or l5
L6            4 L4 OR L5

=> duplicate remove l6
DUPLICATE PREFERENCE IS 'CAPLUS, BIOSIS'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L6
L7            4 DUPLICATE REMOVE L6 (0 DUPLICATES REMOVED)

=> s heparin binding domain
L8         2925 HEPARIN BINDING DOMAIN

=> s (protease nexin-1) or (protease nexin-2) or (antithrombin III) or (heparin cofactor II) or (p
   4 FILES SEARCHED...
L9        37901 (PROTEASE NEXIN-1) OR (PROTEASE NEXIN-2) OR (ANTITHROMBIN III)
                OR (HEPARIN COFACTOR II) OR (PROTEIN C INHIBITOR)

=> s (platelet factor 4) or (bovine pancreatic trypsin inhibitor) or (ghilanten-related inhibitor)
   5 FILES SEARCHED...
L10       12786 (PLATELET FACTOR 4) OR (BOVINE PANCREATIC TRYPSIN INHIBITOR) OR
                (GHILANTEN-RELATED INHIBITOR)

=> s L8 (p) (l9 or l10)
L11         158 L8 (P) (L9 OR L10)

=> s l7 (p) l11
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L72 (P) L65'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L78 (P) L68'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
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FIELD CODE - 'AND' OPERATOR ASSUMED 'L80 (P) L69'
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L82 (P) L70'
L12           0 L7 (P) L11

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     (FILE 'HOME' ENTERED AT 07:20:19 ON 09 DEC 2002)

     FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
     07:21:46 ON 09 DEC 2002
L1          3355 S TFPI OR TFPI-2
L2          1746 S KUNITZ (P) DOMAIN
L3           354 S L1 (P) L2
L4             4 S L3 (P) (CHIMERIC PROTEIN)
L5             2 S L3 (P) (FUSION PROTEIN)
L6             4 S L4 OR L5
L7             4 DUPLICATE REMOVE L6 (0 DUPLICATES REMOVED)
L8          2925 S HEPARIN BINDING DOMAIN
L9         37901 S (PROTEASE NEXIN-1) OR (PROTEASE NEXIN-2) OR (ANTITHROMBIN III
L10        12786 S (PLATELET FACTOR 4) OR (BOVINE PANCREATIC TRYPSIN INHIBITOR)
L11          158 S L8 (P) (L9 OR L10)
L12            0 S L7 (P) L11

=> d l7 1-4 ibib abs

L7   ANSWER 1 OF 4  BIOSIS  COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER:   2001:340475  BIOSIS
DOCUMENT NUMBER:    PREV200100340475
TITLE:              Chimeric proteins.
AUTHOR(S):          Innis, Michael A.; Creasey, Abla A.
                    ASSIGNEE: Chiron Corporation
PATENT INFORMATION: US 6174721 January 16, 2001
SOURCE:             Official Gazette of the United States Patent and Trademark
                    Office Patents, (Jan. 16, 2001) Vol. 1242, No. 3, pp. No
                    Pagination. e-file.
                    ISSN: 0098-1133.
DOCUMENT TYPE:      Patent
LANGUAGE:           English
AB     ***Chimeric***     ***proteins***   possessing   ***Kunitz***  -type
       ***domain***   1 of   ***TFPI***  -  ***2***   and   ***Kunitz***  -type
       ***domain***   2 of   ***TFPI***   are disclosed, as are muteins of
       ***TFPI***   and   ***TFPI***  -  ***2***  . Nucleic acid sequences,
     expression vectors and transformed host cells encoding and capable of
     producing the disclosed   ***chimeric***     ***proteins***   and muteins
     are also disclosed. Finally, methods for prevention and treatment of
     septic shock using the   ***chimeric***     ***proteins***   and muteins
     are disclosed.

L7   ANSWER 2 OF 4  BIOSIS  COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER:   2001:311733  BIOSIS
DOCUMENT NUMBER:    PREV200100311733
TITLE:              Inhibition of endotoxin-induced coagulation in rats by XK1,
                    a potent and selective tissue factor-factor VIIa inhibitor.
AUTHOR(S):          Conricode, Kevin M. (1); LaChance, Rhonda M. (1); Girard,
                    Thomas J. (1)
CORPORATE SOURCE:   (1) Pharmacia Corporation, St. Louis, MO USA
SOURCE:             Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 54a.
                    print.
                    Meeting Info.: 42nd Annual Meeting of the American Society
                    of Hematology San Francisco, California, USA December
                    01-05, 2000 American Society of Hematology
                    . ISSN: 0006-4971.
DOCUMENT TYPE:      Conference
LANGUAGE:           English
SUMMARY LANGUAGE:   English
AB   Sepsis is frequently complicated by disseminated intravascular coagulation
     (DIC) with associated consumption of blood coagulation factors. Animal
     model studies of endotoxin- and bacteria-induced DIC have implicated
     tissue factor (TF) as the trigger for activation of coagulation. We have
     tested the effectiveness of a highly potent and selective inhibitor of
     TF-factor VIIa in reducing endotoxin-induced DIC in rats. This unique
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inhibitor, referred to here as XK1, is a ***chimeric*** ***protein*** which consists of the gla ***domain*** -containing light chain of factor X linked to the first ***Kunitz*** ***domain*** of ***TFPI*** (Science 148:1421-4). Endotoxin-induced coagulation was evaluated by determining plasma thrombin-antithrombin complex (TAT) levels following iv. injection of 0.3 mg/kg LPS into anesthetized rats. In control (vehicle-infused) rats, TAT increased from 0.4 + 0.1 mug/l (mean + S.E.) at baseline to 8.9 + 0.9 mug/l at 120 min after LPS injection and 19.2 + 1.8 mug/l at 180 min (n=17). Infusion of XK1 at 15 mug/kg/min (started 30 min prior to and continued until 180 min after LPS injection) reduced plasma TAT to 2.3 + 0.4 mug/l at 120 min and 13.5 + 2.7 mug/l at 180 min (n=7), while infusion at 60 mug/kg/min further decreased TAT to 1.0 + 0.3 mug/l and 7.8 + 3.0 mug/l at 120 and 180 min, respectively (n=5). Plasma XK1 levels reached approximately 4 mug/ml with the low dose and 25 mug/ml, a concentration which prolongs the prothrombin time of human plasma by more than 10-fold, with the high dose. The consumption of plasma fibrinogen at 240 min after LPS injection was attenuated by the high dose of XK1 (112 + 14 mg/dl versus 134 + 9 mg/dl for control and high dose XK1 groups, respectively; n=4 in each group). Blood loss following tail transection was also increased from 0.132 + 0.022 g with the vehicle (n=13) to 0.319 + 0.042 g with low dose XK1 (n=3) and 0.538 + 0.084 g with high dose XK1 (n=4). We conclude that XK1 at least partially reduces endotoxin-induced coagulation in rats. The possible complete blockade of coagulation by very high doses of XK1 in this model remains to be demonstrated.

L7 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:695173 CAPLUS
DOCUMENT NUMBER: 132:175508
TITLE: Structural requirements for TFPI-mediated inhibition of neointimal thickening after balloon injury in the rat
AUTHOR(S): Han, Xin; Girard, Thomas J.; Baum, Pamela; Abendschein, Dana R.; Broze, George J., Jr.
CORPORATE SOURCE: Division of Hematology/Oncology, Barnes-Jewish Hospital at Washington University Medical Center, St. Louis, MO, 63110, USA
SOURCE: Arteriosclerosis, Thrombosis, and Vascular Biology (1999), 19(10), 2563-2567
CODEN: ATVBFA; ISSN: 1079-5642
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The intimal thickening that follows vascular injury is inhibited by periprocedural tissue factor pathway inhibitor (TFPI) treatment in animal models. TFPI is a multivalent Kunitz-type protease inhibitor that inhibits factor Xa via its second Kunitz domain and the factor VIIa/tissue factor (TF) complex via its first Kunitz domain. The basic C-terminus of TFPI is required for the binding of TFPI to cell surfaces and cell-bound TFPI mediates the internalization and degrdn. of factor X and the down regulation of surface factor VIIa/TF activity. The C-terminus of TFPI is also required for its reported direct inhibition of smooth muscle cell proliferation in vitro. To examine the structural requirements for the inhibition of neointimal formation by TFPI, several TFPI-related proteins were tested in the rat carotid angioplasty model: (1) XK1, a hybrid protein contg. the N-terminal portion of factor X and the first Kunitz domain of TFPI that directly inhibits factor VIIa/TF; (2) TFPIWT, the full-length TFPI mol. that inhibits factor Xa and factor VIIa/TF and binds cell surfaces; (3) TFPIK361, an altered form of TFPI that inhibits factor Xa, but not factor VIIa/TF, and binds cell surfaces; (4) TFPI13-161, a truncated form of TFPI that inhibits factor VIIa/TF but interacts with factor Xa poorly and does not bind to cell surfaces. Seven day infusions of XK1, TFPIWT, and high levels of TFPIK361 begun the day before balloon-induced vascular injury produced a significant redn. in the intimal hyperplasia measured 28 days after angioplasty. The infusion of high concns. of TFPI13-161 was ineffective in this model. These in vivo results directly mirror the ability of each TFPI-related protein to inhibit tissue thromboplastin-induced coagulation in rat plasma: XK1.apprxeq.TFPIWT>TFPIK361>>TFPI13-161. The studies confirm the important role of TF-mediated coagulation in the smooth muscle proliferation and neointimal thickening that follows vascular injury and suggest that the anticoagulant effect alone of TFPI and TFPI-related

proteins is sufficient to explain their therapeutic action.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:295080 CAPLUS
DOCUMENT NUMBER: 124:325361
TITLE: Chimeric proteins and muteins of tissue factor pathway inhibitors TFPI and TFPI-2
INVENTOR(S): Innis, Michael A.; Creasey, Alba A.
PATENT ASSIGNEE(S): Chiron Corporation, USA
SOURCE: PCT Int. Appl., 67 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9604378	A2	19960215	WO 1995-US9464	19950725
WO 9604378	A3	19960314		
W: AU, CA, JP, MX				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5589359	A	19961231	US 1994-286521	19940805
US 5563123	A	19961008	US 1995-437841	19950509
US 5696088	A	19971209	US 1995-436175	19950509
CA 2196290	AA	19960215	CA 1995-2196290	19950725
AU 9531500	A1	19960304	AU 1995-31500	19950725
AU 710535	B2	19990923		
EP 776366	A1	19970604	EP 1995-927478	19950725
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 10503375	T2	19980331	JP 1995-506598	19950725
US 6174721	B1	20010116	US 1997-943682	19971014

PRIORITY APPLN. INFO.: US 1994-286521 A 19940805
US 1995-438184 B1 19950509
WO 1995-US9464 W 19950725

AB ***Chimeric*** ***proteins*** possessing ***Kunitz*** -type ***domain*** 1 ot ***TFPI*** - ***2*** and ***Kunitz*** -type ***domain*** 2 of ***TFPI*** are provided, as are muteins of ***TFPI*** and ***TFPI*** - ***2*** . Nucleic acid sequences, expression vectors, and transformed host cells encoding and capable of producing the disclosed ***chimeric*** ***proteins*** and muteins are also provided. ***Chimeric*** ***proteins*** were constructed with amino acid sequences capable of binding a cell surface component (glycosaminoglycan, heparin) such as peptide moieties from protease nexin-1, protease nexin-2, antithrombin III, heparin cofactor II, protein C inhibitor, platelet factor 4, bovine pancreatic trypsin inhibitor, and ghilanten-related inhibitors. The ***chimeric*** ***proteins*** are produced as yeast .alpha.-factor ***fusion*** ***proteins*** for secretion, or alternatively, may be expressed as a ubiquitin ***fusion*** ***protein*** . Potential sites for N-liked glycosylation within ***TFPI*** (Asn116.fwdarw.Gln, Asn227.fwdarw.Gln) are removed using overlapping PCR and mutations och1, mn1, and alg3 are introduced in transformed yeast cells to prevent the prodn. of .alpha.-1,6-polymannose terminal carbohydrate moieties in the chimeric products. Finally, methods for prevention and treatment of septic shock using the ***chimeric*** ***proteins*** and muteins are described.

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FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 07:21:46 ON 09 DEC 2002
L1 3355 S TFPI OR TFPI-2
L2 1746 S KUNITZ (P) DOMAIN
L3 354 S L1 (P) L2
L4 4 S L3 (P) (CHIMERIC PROTEIN)
L5 2 S L3 (P) (FUSION PROTEIN)
L6 4 S L4 OR L5

L7 4 DUPLICATE REMOVE L6 (0 DUPLICATES REMOVED)
L8 2925 S HEPARIN BINDING [redacted]MAIN
L9 37901 S (PROTEASE NEXIN-1) OR (PROTEASE NEXIN-2) OR (ANTITHROMBIN III
L10 12786 S (PLATELET FACTOR 4) OR (BOVINE PANCREATIC TRYPSIN INHIBITOR)
L11 158 S L8 (P) (L9 OR L10)
L12 0 S L7 (P) L11

=> log y

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